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COMMENT ON THE PROPOSED RULE ON
OCCUPATIONAL EXPOSURE TO INDOOR AIR POLLUTANTS
ISSUED BY
THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

SUBMITTED BY
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CREDENTIALS

My name is Gio Batta Gori. I am director of the Health Policy Center, Bethesda, Maryland, a consulting practice in toxicology, epidemiology, risk assessment, and the formulation of public policy alternatives compatible with health, safety and the common welfare. Until 1988, I was director of the Franklin Institute Policy Analysis Center, leading a similar program of basic and applied research. Before joining the Franklin Institute, I held executive positions from 1968 to 1980 at the National Cancer Institute. From 1972 to 1980 I was Deputy Director of the Division of Cancer Causes and Prevention, with simultaneous responsibilities as Acting Associate Director for the carcinogenesis Program (1976-1978), Director of the Smoking and Health Program (1968-1980), and Director of the Diet, Nutrition and Cancer Program (1972-1980). Before 1972 I served as the Associate Scientific Director of the Division, which is entrusted with developing an understanding of cancer causation, and of the methods for its prevention. I have been directly active in environmental carcinogenesis and health, nutrition and health, non-ionizing radiation and health, and the relationship between smoking and health. For the latter, I received the DHEW Superior Service Award in 1976. Prior to 1968 I held positions of responsibility in industry and academia.

I hold a Doctorate in Biological Sciences from the University of Camerino, Italy, and a Master of Public Health in epidemiology from Hopkins. I am a diplomate of the Academy of Toxicological Sciences, President of the International Society of Regulatory Toxicology and Pharmacology, past member of the Technical Committee and of the Regulatory Affairs Committee of the Society of Toxicology, member of scientific societies and editorial boards, and editor of Nutrition and Cancer, an International Journal. I have authored over 100 scientific papers. My curriculum is attached.

At the invitation of the Tobacco Institute, I offer comment on the Indoor Air Quality Proposed Rule, issued on Tuesday, April 5, 1994 by the Occupational Safety and Health Administration, the U.S. Department of Labor (USOSHA, 1994). What follows represents exclusively my position, and not necessarily the position of the Tobacco Institute.

TERMS OF REFERENCE

My comment is directed to the broad scope of the Proposed Rule, and primarily to the experimental and circumstantial assumptions presented to support claims of carcinogenic, cardiovascular, and other effects of environmental tobacco smoke (ETS), as derived from weak and equivocal epidemiologic reports. In this context, I find it important to review some terms of reference, and especially what rules of evidence may govern the interpretation of available reports.

My comment assumes that regulation must be fair, and so must derive from an objective and not arbitrary determination of facts. The further assumption is that the ultimate scope of the rulemaking process is to produce an objective assessment, so that public decisionmakers may have a factual basis on which to deliberate. Because of this demand for objectivity, and because the Proposed Rule is presented as having a scientific basis, I first recall the standard rules of the scientific method as follows:

- The prediction of natural cause/effect sequences is the cognitive goal of science.
- Science is blind to ethical valuation, because of the subjective determinants of ethics.
- Phenomenological observations (i.e. fact gathering, survey type or fortuitous observations) do not constitute validated knowledge unless fitting in the context of validated theories.
- Experimental observations derive from purposeful experiments that test whether outcomes of cause/effect hypotheses are reproducible or forecastable and may thus become validated predictive theories.
- Valid observations derive only from experiments reproducible under *coeteris paribus* conditions.
- Science has no interest in propositions that cannot be tested.
- The validity of a theory is confined to the experimental conditions under which its predictivity was tested.

- A theory is provisionally validated only if its predictions are either sufficient or necessary for the predicted outcome to occur. If not, competing hypotheses must be explained before validation is possible.
- The cognitive value of a theory --i.e. its objectivity -- is determined by the reliability and precision of its predictivity. Cognitive sufficiency is attained when the reliability and precision of predictivity reach probability expectations that warrant experimental or operational success in technology or policy.

The experimental references mentioned in the Proposed Rule are descriptive exercises in analytical chemistry, *in vitro* studies, chronic and acute animal studies, and short term studies in humans. They are claimed to endorse the plausibility of a selective interpretation of weak and contradictory epidemiologic reports. In reality, and from the rules above, a scientific evaluation restricts their meaning to the heuristic conditions of the experiments proper, while their support of alleged adverse health effects of ETS can only be hypothetical and empty of cognitive meaning. On logical grounds and because of their remoteness from human experience, their applicability is usually less permissible than the epidemiologic inferences advanced against ETS, which are themselves based on precarious conjectures.

Most of the epidemiology of chronic multifactorial diseases has not adapted to the scientific method. Observational studies -- the basis of epidemiologic arguments in the Proposed Rule -- encounter especially vexing logical difficulties to individual or synthetic inferences in their interpretation. Here is Rothman's comment on this particular problem:

Despite philosophic injunctions concerning inductive inference, criteria have commonly been used to make such inferences. The justification offered has been that the exigencies of public health problems demand action and that despite imperfect knowledge causal inferences must be made." (Rothman, 1986, p.17).

Clearly, the exigencies of public health represent imperatives that are political and not scientific, and thus raise issues of conduct for scientists assigned to provide decision-makers with a factual basis for action. Which rules of evidence should they adopt if the scientific method cannot be applied? Could they still be objective -- and credible and fair -- by applying contingent and thus arbitrary rules of evidence?

Raised first some 30 years ago, these questions have been compromised in a set of judgmental guidelines – the criteria mentioned by Rothman above – initially proposed in the first Surgeon General's report on smoking and formulated shortly after by Sir A. Bradford Hill (Hill, 1965). They are now familiar considerations in *attempting* to distinguish potentially causal from non-causal associations: strength, consistency, specificity, temporality, response gradient, plausibility, coherence, analogy, and experimental evidence.

On this basis, judgmental inferences of causality have been advanced in situations that substantially met most of these qualifiers. However, methodological difficulties in the epidemiology of multifactorial diseases have identified additional obstacles to causal inferences, also described by Rothman and well known to experienced epidemiologists, but not sufficiently understood outside the profession. These difficulties have persuaded prominent epidemiologists that relative risk values less than 3 could not be used to infer causality because of the irreparable effects of biases and confounders (Wynder, 1987; Rothman, 1982).

When not even the logically compromised "causality criteria" enable inferences of causality, still more elastic ways have been sought in what is ambiguously defined as the "weight of evidence" approach. In theory, this approach entails a loose integration of the pros and cons of a situation -- in the case of the Proposed Rule, for instance, the increased, *decreased*, and *null* risk reports from the reviewed epidemiologic studies. In fact, however, the rules of this approach are absolutely vague and have permitted all sort of arbitrary selectivity (USEPA, 1992c).

On the reasonable assumption that the compilers of the epidemiologic arguments in the Proposed Rule are familiar with the foregoing considerations, it is apparent that their analysis was based neither on scientific standards of evidence nor on the relaxed *causality criteria* of Sir A. Bradford Hill. The compilers would likely declare to have followed a weight of evidence approach, yet it is also undeniable that weights were selectively chosen, with emphasis on signals of increased risk and studious exclusion of null and reduced risk signals, despite equivalent observational validity. The use of selected experimental reports to shore up equivocal epidemiologic accounts further weakens this "weight of evidence" approach, and more so when it is implied that such reports are "scientifically" relevant to the analysis at hand, when in fact they are not.

COMMENT SUMMARY

In order to address possible concerns of *ex parte* influences on my comment, I find it compelling to avoid conjecture and judgment, to focus on issues that are tested or testable, and therefore to adopt standard scientific criteria of evidence.

On this basis, it is necessary to conclude that a universal smoking ban in workplaces is not justified or warranted, because scientifically justified evidence of ETS-associated risks is unavailable. Although affected by subjective psychosomatic and cultural determinants, the issues of irritation and annoyance need nevertheless be addressed as a matter of civic courtesy. In this context, separation of smokers and nonsmokers may be desirable whenever feasible, although adequate ventilation standards are likely to be fully remedial of any conceivable situation. The following highlights my comment:

* Most components of side-stream smoke (SSS) -- the main source of ETS -- become so diluted as to be undetectable by the most sophisticated analytical techniques. Average concentrations of measurable SSS residues in workplace environments are extremely small. Moreover, measurable SSS components are present in ETS at concentrations from one thousand to one million times less than OSHA's own PEL/TLV/TWA regulatory standards for such similar mixtures as coke oven emissions.

* The pathogenic potential of ETS is imponderable even by theoretical considerations. Its contribution to IAQ is insignificant, especially when compared to other factors such as building materials and equipment emissions, work related contaminants, anthropogenic emissions, microbiological contaminants and outdoor air contributions. Air purification and ventilation standards that would adequately control for these major factors in IAQ would further dissolve any conjectural role of ETS.

* The Proposed Rule cites experimental results in animals that are -- for at least two major reasons -- of no demonstrable relevance to possible field effects of ETS in humans. First, the genetic, physiologic, metabolic, anatomic, and behavioral differences make most animal data of unknown relevance to humans, beyond generic effects of acute toxicity. Second, by necessity most studies expose animals to smoke or smoke components under conditions that have little in common with human ETS exposures. In general, exposures are to main-stream or side-stream smoke, at concentrations that are

much higher than typical ETS, and under extremely stressful circumstances. Besides, when human data are directly available there is no good reason to rely on animal reports.

* Prominent researchers in the field consider tobacco smoke a promoter rather than a direct carcinogen -- promoters being generally regarded to be effective only above certain dose thresholds. The epidemiologic record of active smoking supports a threshold at a daily dispersed dose equivalent to 4-5 cigarettes of average pre-1960 yield, at which level active smoking does not appear associated with significant adverse effects. Such a threshold is several thousand times greater than typical doses of ETS exposure.

* By and large, diseases have been tentatively associated with ETS exposure on a proxy basis, namely because of the associations noted for active smoking. However, the diseases in question are multifactorial and the contribution of ETS can only be hypothetical, given the greater and compounded significance of other factors. Unless all significant factors can be accurately controlled -- which may not be technically feasible -- the noise-to-signal ratio would be small and the results uninterpretable. For this reason, epidemiologic studies attempting to link ETS exposure and disease are doomed to produce the equivocal results reported in the literature.

ETS AND ACTIVE SMOKING

The Proposed Rule offers recurring inferences based on the similarities of ETS and the main-stream smoke inhaled by active smokers. It is necessary therefore to recall the available evidence regarding the vast differences of exposure and dose of the two smokes. Also, ETS concentrations typical of the epidemiologic situations studied are thousands of times below permissible exposure levels (PELs) for complex mixtures -- such as coke oven emissions -- regulated in the workplace by the US Occupational Safety and Health Administration, and thousands of times below what appear to be no-effect levels of active smoking exposures (Gori and Mantel, 1991).

Environmental tobacco smoke (ETS) comes from the dilution of side-stream smoke produced by smoldering cigarettes, and from the small residues of main-stream smoke exhaled by active smokers. Generated and existing under much different conditions,

these different smokes have some similarities but marked differences in chemical and physical composition and behavior. All comprise a gas phase, and small respirable suspended particles (RSP). These particles in turn may contain at various times different amounts of water and other volatile components that may exchange with the gas phase.

Main-stream smoke -- inhaled directly by smokers -- is concentrated and confined to the moist environment of mouth, throat, and lung. Its higher gas phase concentrations favor larger respirable particles that condense and retain more water and volatiles. By contrast, ordinary ETS is over 100,000 times more diluted, with much lower humidity and extremely low concentrations of volatiles. Evaporation is faster from ETS particles, which -- within fractions of a second from their generation -- attain sizes 50 to 100 times smaller in mass and volume than their main-stream counterparts. As ETS ages, it undergoes oxidative and photochemical transformations, polymerizations from loss of water and volatiles, reactions with other environmental components, and other changes (NAS, 1986; USSG, 1986; USEPA, 1992c; Guerin et al, 1987; Baker and Proctor, 1990).

From several thousand components of main-stream smoke, Hoffmann and Hecht have selected some 40 agents suspected of being carcinogenic in experimental animals (Hoffmann and Hecht, 1989). In general, however, these agents have shown carcinogenicity in animal organs other than the lungs, at doses much larger than smokers can experience, and with clear and repeated evidence of no-observable-effect-level (NOAEL) doses. At the same time, main-stream and side-stream smoke contain equally large numbers and concentrations of known suppressors of carcinogenesis, present at dose ratios similar to those found effective in suppressing experimental cancer (Rodgman, 1992; Teel and Castonguay, 1992; Van Duuren, 1980).

Of the several thousand components identified in main-stream smoke, only 100 or so have been detected in side-stream smoke under field conditions, due to extreme dilutions. Because of even greater dilution, fewer than 20 ETS components have been identified directly under field conditions. In natural settings, most ETS components are far below the sensitivity of current analytical capabilities (Guerin et al, 1987; Baker and Proctor, 1990). Indeed, the compilers of reports from the National Academy of Sciences (NAS, 1986), the US Surgeon General (USSG, 1986) and the Environmental Protection Agency (USEPA, 1992c) have been forced to infer the presence of ETS components by proxy, based on the composition of the side-stream smoke from which ETS primarily derives.

Nominally, then, ETS and main-stream smoke may share some components, but their chemical and physical differences are substantial. Moreover, the presence of most ETS components can only be postulated because they are beyond material detection. The available evidence offers some limited opportunities to gauge ETS exposures and doses in relation to active main-stream-smoking counterparts.

ESTIMATING ETS EXPOSURE

A major limitation of epidemiologic studies on ETS has been the unreliable estimates of dose, which compound the uncertainties of personal or proxy recall of the intensity, frequency, and duration of exposures over individual lifetimes. Even the simple dichotomous classification of exposed and non-exposed subjects presents recognized uncertainties, such as those deriving from the self-classification of some smokers as non-smokers (USEPA, 1992c; Lee, 1992, 1993). On comparatively more solid grounds, a range of probable momentary exposures to ETS can be inferred from physical and chemical derivations. These inferences are also insufficient to determine cumulative exposures, but raise compelling doubts about the reliability and meaning of epidemiologic estimates.

On the basis of extrapolations from side-stream and main-stream smoke data, the National Academy of Sciences calculated that for nicotine alone the difference in peak inhalation concentrations between smokers and ETS exposed non-smokers varies between 57,000 and 7,000,000 fold (NAS, 1986). Dose estimates based on body fluid concentrations of nicotine or cotinine yield higher values, but depend on environmental and pharmacokinetic assumptions of unlikely validity (USEPA, 1992c), a condition also recognized in the Proposed Rule in its request for pharmacokinetic data at low doses and low blood levels (USOSHA, 1994).

Estimates of exposure to other ETS components are even more problematic because of numerous sources external to ETS. For instance, plasma concentrations of volatile organics in nonsmokers appear to be as much as 2/3 of the corresponding levels in active smokers – an indication of significant sources other than tobacco combustion (Angerer et al, 1992; Brugnone et al., 1992; Perbellini et al., 1988).

By utilizing surrogate side-stream smoke values, conceivable ETS exposure has been compared with current federal standards of permissible occupational exposure to several smoke components. Considering an unventilated room of 100 m³ (3,533 cubic feet), the number of cigarettes that would have to be burned before reaching official threshold limit values varies among 1,170 for methylchloride to 13,300 for benzene, to 222,000 for benzo(a)pyrene, to 1,000,000 for toluene (*Table 1*)(Gori and Mantel, 1991).

Table 1. Estimated number of cigarettes required to reach TLV levels from sidestream smoke emission of selected chemicals in a sealed and unventilated 100 m³ enclosure (Gori and Mantel, 1991).

| SSS Component | SSS output* mg/cigarette | TLV** mg/m ³ | Cigarettes required |
|-----------------|-----------------------------|----------------------------|------------------------|
| Methylchloride | 0.88 | 0.30 | 1,170 |
| Hydroquinone | 0.16 | 2.00 | 1,250 |
| Cadmium | 0.0007 | 0.01 | 1,430 |
| Acetaldehyde | 1.26 | 180.00 | 1,430 |
| Acetic acid | 1.50 | 25.00 | 1,660 |
| Nitrogen oxides | 2.80 | 50.00 | 1,780 |
| Formic acid | 0.525 | 9.40 | 1,790 |
| Pyridine | 0.39 | 16.00 | 4,100 |
| Phenol | 0.25 | 19.00 | 7,600 |
| Methylamine | 0.1 | 13.00 | 13,000 |
| Benzene | 0.24 | 32.00 | 13,300 |
| Catechol | 0.14 | 23.00 | 16,500 |
| Nickel | 0.0025 | 1.00 | 40,000 |
| Dimethylamine | 0.036 | 18.00 | 50,000 |
| Hydrazine | 0.00009 | 0.13 | 145,000 |
| Acetone | 1.00 | 1780.00 | 178,000 |
| Benzo(a)pyrene | 0.00009 | 0.20 *** | 222,000 |
| 2-Toluidine | 0.003 | 9.00 | 300,000 |
| Polonium 210 | 0.4 pCi | 3 pCi/l**** | 750,000 |
| Toluene | 0.000035 | 375.00 | 1,000,000 |

* Data from EPA 1990a, Table C-2, page C-19,20.

** Data from ACGIH 1990.

*** Based on the TLV for coal tar pitch volatiles.

**** EPA 1990b.

The Proposed Rule remarks that comparing ETS with official PEL values may not be feasible because PEL values are intended for single agent exposures and not for mixtures. This distinction, however, is invalid for two reasons. First, workers are never exposed to single agents but to mixtures in any environment, whether workplace or not. Second, valid parallels can indeed be made for PEL values issued for mixtures -- such as coke oven emissions -- that share similar components with side-stream smoke and presumably with ETS, as the Proposed Rule suggests.

In any event, the measurement of ETS respirable particles (ETS-RSP) has been more fruitful than the measurement of single chemical species. Methods have been devised that separate particles that may derive from ETS and other sources.

Use of these methods yields the current consensus -- supported by EPA's reports on ETS -- that prevailing concentrations of ETS-RSP are below 50 µg/m³ in households with smokers, the environments studied in most epidemiologic studies that have suggested elevated risks (*Table 2*)(USEPA, 1992c; Gori and Mantel, 1991; Samet, 1992; Steenland, 1992).

Table 2. Some reports of concentrations of respirable suspended particles from ETS and other sources in various environmental settings with and without smoker presence. (Gori and Mantel, 1991).

| Reference | Site | RSP Concentration $\mu\text{g}/\text{m}^3$ | |
|----------------------|----------------|---|---------|
| | | No smoking | Smoking |
| Coultas et al. 1990 | Homes | NA | 17 |
| Sheldon et al. 1989 | Homes | 22** | 65** |
| Spengler et al. 1981 | Homes | NA | 20 |
| Spengler et al. 1985 | Offices | 39* | 72** |
| Proctor et al. 1989b | Offices | 8* | 23* |
| Oldaker et al. 1990 | Offices | NA | 27* |
| Miesner et al. 1988 | Offices | 15** | 36** |
| Sterling et al. 1983 | Offices | 15** | 29** |
| Coultas et al. 1990b | Workplaces | NA | 64** |
| Oldaker et al. 1990 | Restaurants | NA | 36* |
| Crouse 1988 | Restaurants | NA | 34* |
| Proctor 1990 | Public transit | 14* | 36* |

* Based on UV-RSP portion of total RSP

** Based on total RSP

NA - Data not available or not applicable

Because of aerodynamic size and other differences, EPA recognizes that only about 10% of inhaled ETS-RSP may be retained by non-smokers, compared to nearly 90% for main-stream smoke RSP in active smokers (USEPA, 1992c). Furthermore, lung clearance is faster and more efficient in non-smokers than in smokers (Gori and Mantel, 1991), and target cell doses are far smaller because of greater lung surface at the greater depths reached by ETS-RSP (Mercer and Crapo, 1993).

Overall, these considerations lead to the conclusion that the prevalent ETS-RSP dose is minuscule. Although difficult to define, it is at least 100,000 times smaller than the main-stream smoke dose in active smokers, as official EPA reports acknowledge (1,7,8).

For the average ETS-exposed individual, this estimate translates into an annual dose equivalent to far less than the main-stream RSP of 1 cigarette evenly dispersed over the 12 month period (Table 3)(Gori and Mantel, 1991).

Documented observations -- also plainly perceived in everyone's life and experience -- indicate that people have innate capacities to cope with multiple low-level exposures. The question, then, is whether very small doses of ETS pose plausible risks to non-smokers.

COULD MINUTE ETS EXPOSURES POSE A HEALTH RISK?

Because direct measurements of the biologic activities, exposures, and doses of ETS are so problematic, initial attempts have inferred ETS-linked health risks by arithmetic derivation from the apparent risks associated with active smoking. This approach was both supported and opposed in a recent EPA review (USEPA, 1992b). The review

Table 3. Relative dose estimate of respirable suspended particulates (RSP) in typical active smokers and ETS exposed non-smokers.

| | |
|---|---|
| ACTIVE SMOKER | 30 cigarettes per day 15 mg RSP inhaled per cigarette 90% lung retention efficiency DAILY DOSE about 400 mg |
| ETS EXPOSED NON-SMOKER | 0.05 mg RSP/cubic meter of air 1.5 hours per day exposure (*) 0.7 cubic meters per hour inhaled 10% lung retention efficiency DAILY DOSE about 0.00525 mg |
| CRUDE DOSE RATIO 0.00525: 400 about 1: 75,000 | |
| Lung surface permeability some 3 times greater in smokers Lung clearance some 3 times more efficient in smokers ETS dose distributed over greater surface deeper in lungs | |
| NET DOSE RATIO AT TARGET TISSUE < 1: 500,000 | |

(*) USOSHA, 1994; Emmons et al., 1992.

dedicates a chapter to the proposition that: "...due to the similarity in chemical composition between [main-stream smoke] and ETS and the known human exposure to ETS..., ETS would also be classified as a...human carcinogen "(p.4-10). Elsewhere, the review lists the many differences of main-stream smoke and ETS, suggesting that risk extrapolation from active smoking may not be feasible (p.2-7). A direct comparison also has been questioned by other ETS opponents, citing the obvious contrasts (Steenland, 1992). In reality, the only reasonable inferences would come from the foregoing estimates. Accordingly, the health risks of ETS -- if any -- would have to be so much smaller as to be unmeasurable, when compared to the risk associations of main-stream smoke.

Although the main-stream smoke that active smokers inhale contains substances that are carcinogenic in animal experiments, the epidemiology and pathogenesis of lung cancer suggests that smoking may act as a promoter rather than as a direct carcinogen (Doll, 1978; Doll and Peto, 1978; Klawansky and Fox, 1984; Altshuler, 1989; Albert, 1989). Promoters are universally regarded as being effective only above a certain dose threshold, and active smoking is no exception.

For main-stream active smoking the epidemiologic risks associated with certain diseases become non-significant at low exposures. Persons who inhale a daily dispersed dose equivalent to 4-5 cigarettes of pre-1960 yields may not attain health risks significantly different from those of non-smokers (*Tables 4-6*) (Gori, 1976; Gori and Mantel, 1991).

Table 4. Maximum levels of daily cigarette consumption at which lung cancer risk in male smokers may not be significantly increased from the risk of non-smokers (Gori and Mantel, 1991).

| Reference | Max. Cigarettes/day |
|----------------------|---------------------|
| British Doctors* | 6.3 |
| Swedish Men** | 3.9 |
| ACS 9 States*** | 5.4 |
| ACS 25 States** | 0.9 |
| US Veterans*** | 0.6 |
| Canadian Veterans*** | 1.6 |
| Japanese Men** | 3.1 |
| California Men*** | 7.0 |

* From Doll and Peto, 1978

**From USSG, 1979, page 5-13 table 2.

***From USSG, 1982, page 38 table 6.

Table 5. Maximum levels of daily cigarette consumption at which risk for coronary heart disease mortality in male smokers may not be significantly increased from the risk of non-smokers, based on epidemiologic data (Gori and Mantel, 1991).

| Reference | Max. Cigarettes/day |
|-------------------|---------------------|
| U.S. Veterans | 1.5 |
| ACS 9 States | 2.5 |
| Japanese Men | 4.0 |
| Canadian Veterans | 4.5 |
| British Doctors | 4.5 |
| Swedish Men | 2.5 |
| California Men | 3.0 |
| Swiss Physicians | 3.0 |

* Epidemiologic data from USSG, 1983, p.118.

No-effect observations at comparatively high doses are also routinely reported in experimental animal exposure to whole smoke or its fractions. In a recent evaluation of smoking and health issues, the Congressional Research Service of the Library of Congress stated as follows:

"The existence of an exposure threshold for disease onset below which many passive smokers fall is not implausible. Most organisms have the capacity to cleanse themselves of some level of contaminants. It is for this reason that public policy usually does not insist that every unit of air or water pollution be removed from the environment...In fact, strongly nonlinear relationships in which health effects rise with the square of exposure, and more, have been found with respect to active smoking (see Surgeon General's Report, 1989, p.44). Were these relationships projected backwards to construct the lower (unknown) portion of the health effect/physical damage function, the observed relationship might lead researchers *a priori* to expect no empirical relationship. Thus, the issue raised by this potential break in the causative chain is whether researchers should expect to find a significant relationship between passive smoking and health effects." (Gravelle and

Table 6. Maximum levels of daily cigarette consumption at which risk for respiratory disease mortality in male smokers may not be significantly increased from the risk of non-smokers, based on epidemiologic data (Gori and Mantel, 1991).

| Reference | Max. Cigarettes/day |
|---------------------------------|---------------------|
| <i>Chronic Bronchitis</i> | |
| U.S. Veterans | 5.5 |
| Canadian Veterans | 2.6 |
| <i>Emphysema</i> | |
| U.S. Veterans | 2.2 |
| Canadian Veterans | 2.7 |
| California Men | 5.5 |
| <i>Bronchitis and Emphysema</i> | |
| British Doctors | 3.0 |

* Epidemiologic data from USSG, 1984, p.202.

Zimmermann, 1994, page 45). (Italics in text, bold emphasis added).

The presence of no-observable-effect-levels (NOAELs) for active smoking should have a disposing relevance in the evaluation of claimed health risks of ETS exposure. Such NOAELs become apparent in routine extrapolations from epidemiologic dose/response data (Gori, 1976; Gori and Mantel, 1991), as well as from the direct evidence of epidemiologic studies.

A compendium of 34 year follow-up data was recently published for the prospective Framingham study, the longest and most closely monitored epidemiologic study of its kind in the United States (Freund et al, 1993). The report states: "For all CHD

[coronary heart diseases] a clear relationship exist only for younger men. Women may have a slightly increased risk below age 65, while no relationship is seen for men or women past age 65." However, for any smokers of 1-10 cigarettes/day the age adjusted rates are generally *below* the rates of nonsmokers. Age adjusted rates are also unchanged for lung cancer in nonsmokers and any smokers of 1-10 cigarettes/day below age 65. These reports are consonant with previous reports from the Framingham trial.

A large Swedish study also reported no correlation between smoking and cardiovascular illness (Lapidus, 1985). The British Doctors study in England is widely regarded as the best continuing study outside the United States, and perhaps the best in the world. A 1980 paper reported on mortality rates in female British doctors after 22 years of observation (Doll et al., 1980). There was no increase in mortality rates at any level of daily cigarette consumption for pulmonary heart disease. For ischemic heart disease and lung cancer, mortality rates were the same in nonsmokers and in smokers of 1-14 cigarettes/day. Mortality for all diseases was actually slightly lower in smokers of 1-14 cigarettes/day than in non-smokers.

For male British doctors, mortality rates in the group smoking 1-14 cigarettes/day were slightly elevated after 20 years of observation (Doll and Peto, 1976). However, extrapolation from dose/response functions indicate that mortality for lung cancer, cardiovascular and respiratory diseases would not be elevated for smokers inhaling an evenly dispersed daily dose equivalent to 5-6 pre-1960 cigarettes (*Tables 4-6*)(Gori, 1976; Gori-Mantel, 1991). The male/female difference in NOAELs - expressed as cigarettes smoked daily -- is likely a reflection of a more aggressive smoking behavior by male doctors, who would inhale more smoke from similar numbers of cigarettes.

A study by the National Center for Health Statistics found that patterns of heart diseases and ischemic heart diseases did not parallel patterns of smoking habits in different United States regions (Gillum, 1994). Another recent study reports that cigarette smoking fails to explain international differences in mortality for chronic obstructive pulmonary diseases (Brown et al., 1994).

A recent study by the National Cancer Institute reported that smoking less than 15 cigarettes/day was associated with a reduction ($RR=0.6$) of cancers of the nasal cavity and paranasal sinuses (Zheng et al., 1993). This matches earlier reports of decreased risk for cancers of the oral cavity for smokers of less than 20 cigarettes/day (Wynder et al., 1957; Keller, 1967).

To these reports one should add the generally accepted evidence that moderate pipe and cigar smoking are not associated with increased risks of lung cancer, cardiovascular, and respiratory illnesses. On this basis, it has been suggested that nicotine and carbon monoxide are unlikely to have adverse cardiovascular effects, since their blood levels are quite similar in cigarette, pipe, and cigar smokers (Wald et al., 1981). Significantly, this conclusion about the safety of nicotine at the doses experienced by active smokers was also echoed officially by the Independent Scientific Committee on Smoking and Health of the United Kingdom (Froggatt, 1988).

As mentioned above, other studies have reported NOAEL estimates, obtained by regression analysis of dosimetry data from the major epidemiologic studies listed by the Surgeon General's Reports (*Tables 4-6*). According to this evidence, a level of consumption equivalent to the dose of some 4-5 cigarettes/day (average pre-1960 yields) appears compatible with no significant elevations of risk for lung cancer, cardiovascular and respiratory diseases (Gori, 1976; Gori and Mantel, 1991).

The evidence for NOAEL thresholds is not confined to disease outcome data in epidemiologic studies: it is also generally apparent in studies of the biomarkers and risk factors that are thought to have a pathognomic role.

In considering exposure, it should be kept in mind that many cigarette smoke components are also introduced in the environment from a variety of other sources, and that endogenous toxicants are produced in large numbers by normal physiologic functions (Ames and Gold, 1991; Angerer et al., 1992).

In this context, the meaning of the mutagenicity associated with smoking remains speculative. Extensive studies by the National Toxicology Program and other researchers have failed to validate mutagenicity as a predictor of carcinogenicity in animal bioassays or in man (Ashby and Tennant, 1991; Zeiger et al., 1990; Tennant, 1988).

Studies have also shown that the mutagenicity of smokers's urine is elevated only in smokers of over 10 cigarettes/day, offering other evidence of a threshold effect (van Doorn et al., 1967; Mohtashamipur et al., 1985). More recent studies report that -- although mutagenic -- cigarette smoking may actually protect against additional genotoxic insults (Oesch et al., 1994).

A review by the International Agency for Research on Cancer listed 10 studies that could not find differences in sister chromatid exchange (SCE) frequencies in peripheral lymphocytes of smokers and non-smokers, while studies reporting a dose/response gradient were consistent with a NOAEL threshold for smoking less than 10 cigarettes/day (IARC, 1986, pp.191-192). The situation has been confirmed by a more recent study of SCE frequencies in ETS exposed subjects (Gorgels et al., 1992). Significantly, studies report that aborted fetuses from smoking mothers have 40% less chromosomal abnormalities than fetuses from non-smoking mothers (Kline et al., 1993), while other studies report that maternal smoking is associated with a much *decreased* risk of mongoloid retardation or Down syndrome (Kline et al., 1993; Cuckle et al., 1990).

In general, no association was found between 4-aminobiphenyl-hemoglobin adducts, pack years of smoking, and cancer diagnosis (Weston et al., 1991). Following nuclease P1 enrichment techniques, DNA adducts were detected in oral tissues, but the adduct burden in smokers of 1-10 cigarettes/day was not different from the burden in non-smokers, giving another confirmation of threshold (Jones et al., 1993). Studies of human lung cancer tissues found that serum cotinine levels and adduct levels were not corre-

lated, and could detect adducts only in 7 of 38 individual tumor samples (Shields et al., 1993). DNA adducts of aromatic hydrocarbons in lymphocytes were not found to correlate with smoking habits (van Schooten et al., 1992; Grzybowska et al., 1993). DNA adducts were at similar levels in sperm cells of smokers and nonsmokers, a finding of interest given the intense DNA replication in spermatogenesis (Gallagher et al., 1993). Equal similarities were reported for DNA adducts of cervix tissues (King et al., 1994).

In regard to cardiovascular issues, current thinking holds that increased blood clotting capacity may explain the association of heavy smoking and cardiovascular events. However, the Framingham study reports an absence of cardiovascular risks for smokers of 1-10 cigarettes/day, consonant with an immaterial change in mean fibrinogen (about 1%) in smokers of less than 1 pack of cigarettes/day (Kannel et al., 1987). It has been suggested that two eicosanoids, prostacyclin and thromboxane A₂ are increased in smokers, but studies indicate no change in smokers of less than 10-15 cigarettes/day (Wennmalm et al., 1991). The large and well known Kuopio cohort prospective study in Finland found a correlation of plasma fibrinogen levels with several psychosocial and socioeconomic variables, but not with smoking (Wilson et al., 1993).

The Framingham Offspring Study and a Kaiser Permanente study report that cigarette smoking was not correlated with Lipoprotein(a) levels (Jenner et al., 1992; Selby et al., 1994). Between 1981 and 1990, an evaluation of 11,199 randomly selected subjects in new England found no association of smoking and dyslipidemic hypertension (Eaton et al., 1994). The British Regional Heart Study, a large prospective study of 7735 men aged 40-59, reported on alcohol drinking, smoking and cholesterol levels, concluding that "current smokers who were heavy drinkers or non-drinkers had the lowest mean cholesterol levels" (Wannamethee and Shaper, 1992). A Japanese study also found no difference in plasma cholesterol between smokers and nonsmokers (Imaizumi et al., 1991). A study of 51,723 participants of community-based cholesterol screening clinics in 10 US cities found no association between active smoking and plasma cholesterol levels in men and women over age 60, and no elevation of plasma cholesterol for younger subjects smoking less than 10 cigarettes/day (Muscat et al., 1991).

The Cardiovascular Health Study Collaborative Research Group reports that in a cohort of 5201 men and women over 65 years of age, cigarette smoking was a *negative* predictor of blood pressure, confirming a number of prior reports (Tell et al., 1994). A recent collaborative study of the Center for Disease Control of the US Department of Health

and Human Services found that coronary occlusion was inversely correlated with levels of high density lipoproteins (HDL), but unrelated to smoking (Freedman et al., 1994). In China, coronary mortality is some 10 times less frequent than in Germany, although the prevalence of smoking is 70% in China versus 37% in Germany. Total cholesterol, however, is much higher in German than Chinese subjects (Stehle et al., 1991). Yet, also in Germany, the prevalence of most CVD risk factors increased considerably during a period of substantial mortality declines (Hoffmeister et al., 1994). Anomalies such as these have led prominent clinicians to conclude that total and low density lipoprotein (LDL) cholesterol may be the only demonstrable CVD risk factor (Roberts, 1989).

These considerations support directly the notion of smoking NOAELs in cardiovascular diseases. In fact, the National Cholesterol Education Program only lists smoking of over 10 cigarettes/day as a possible risk factor (NCEP, 1988).

In regard to respiratory diseases, early reports of forced respiratory volume (FEV_1) and forced vital capacity (FVC) deficits in smokers are still compatible with NOAEL thresholds below 10 cigarettes/day (Dockery et al., 1988; Sorlie et al., 1986). The Multiple Risk Factor Intervention Trial (MRFIT) tested 6347 males randomly distributed in a usual care group (control) and a special intervention group that included an intensive and substantially successful smoking cessation program. During a 6-7 year follow-up, forced expiratory volume (FEV_1) measures were similar in the two groups, a finding that confirms reports from previous studies (Browner et al., 1992).

A threshold effect at some 10 cigarettes/day was also reported for emphysema in asthmatic patients (Kondoh et al., 1990). Elastin peptide concentration in circulation has been suggested as a marker of lung elastin degradation and thus of emphysematous changes. A recent study found no correlation between elastin peptide concentration and smoking (Frette et al., 1994). Another study found no increased severity of microscopic emphysema with increased daily cigarette consumption (Gillooly and Lamb, 1993). More recently, a high resolution computed tomography study of patients with interstitial lung disease reported no correlation of smoking with either the disease or emphysema (McDonagh et al., 1994).

In this light, prevalent ETS exposures equivalent to less than the active smoking of one cigarette per year are thousands of times below exposures that result in no significant health risks for active smokers. In order to exceed these thresholds, the specific biologic

activity of ETS would have to be thousands of times greater than for main-stream smoke -- clearly an untenable proposition. Altogether, consideration of the vast exposure and dose differentials give clear indication that ETS could not pose ponderable health risks, even assuming that ETS may be chemically and biologically equivalent to main-stream smoke. Experimental reports in man or animals do not contradict, and many actually sustain this conclusion.

EXPERIMENTAL STUDIES

This section addresses experimental hypotheses and citations mentioned in the Proposed Rule and not considered in the sections above. In general, these items concern active smoking and are presented by the Proposed Rule with an eye to sustaining the plausibility of inferences of ETS risk. The implied injunction that threshold effects are not to be considered is obviously not warranted in view of the direct evidence for thresholds presented above.

It should be kept in mind that animal experiments are set up for maximum effect, and hence push dosages to the extremes compatible with survival. Most studies, for instance, cause COHb blood levels as high as 40% in treated animals, a condition that finds not even close parallel in human smokers. Also, experimental studies have utilized animals whose reactions to high doses of main-stream smoke, ETS, or their components are ostensibly of unknown relevance to human responses, given profound differences in smoke generation and exposure conditions, and in anatomy, physiology, and metabolism. In the end, there is no doubt about potential pathogenic effects of cigarette smoke administered at extremely high doses to animals. At the same time, it is equally clear that the interpretation of such effects in equivalents human terms requires inferences that are unwarranted by the profoundly different conditions under which they are obtained. In fact, such inferences become wholly unnecessary when considering potential ETS effects, because of the wealth of human observations compatible with no-effect levels for active smoking.

Pulmonary. Chronic cigarette smoking may increase alveolar macrophages (AM) and polymorphonuclear (PMN) leukocytes, but the pathogenic significance of such increases -- if any -- remains an open question (Ludwig et al., 1995). The conjecture that AM

and PMN elevation may increase elastase in experimental animals is not sustained by direct observations in human smokers, as noted above (Frette et al., 1994; Gilooly and Lamb, 1993; McDonagh et al., 1944). Even less clear is the meaning of a possible decrease of AM-ATP and of changes in the permeability of respiratory epithelium in Guinea pigs (Burns et al., 1989). Notably, all such changes have been obtained after exposure of animals or tissues to main-stream smoke at concentrations orders of magnitude higher than typical ETS.

The Proposed Rule also mentions the Olson (1985) study reporting increased ornithine decarboxylase activity in rat tracheas; however the study fails to show increased activity in the lungs, and no effect whatsoever is noted at the 10% side-stream smoke dose, despite considerable exposure documented by carboxyhemoglobin levels around 6%.

Also, because they could both inactivate and activate electrophiles of concern, the pathognomic meaning is still a matter of conjecture in regard of the induction of such polymorphic enzymatic systems as cytosolic glutathione S-transferase, P450 cytochromes for aromatic hydrocarbons and debrisoquine -- aryl hydrocarbon hydroxylases (AHH) or microsomal mono-oxygenases (MMO) -- and the arylamine acetylators. The interpretation of their significance is further complicated by a multitude of genetic controls and determinants in specific phenotypes (Ketterer et al, 1992; Anttila et al. , 1992; Bartsch et al., 1992; Caporaso et al., 1992; Vineis and Ronco, 1992). For instance, the Proposed Rule mentions that main-stream and side-stream smoke can induce pulmonary aryl hydrocarbon hydroxylase (AHH) activity. The Gairola (1987) study is cited, but no mention is made that such induction happened in mice and rats but not in Guinea pigs, the latter actually experiencing a small reduction of activity, a finding confirmed by other studies and in other animal species (Bilimoria et al., 1977; Lubawy and Isaac, 1980). In any event, HHA-MMO activity may be necessary to both activate and deactivate xenobiotics, and therefore the significance of such changes remains moot.

The Proposed Rule also mentions a study of passive smoking in young lambs (Stecenko et al., 1986). The study, however, generated "ETS" in a questionable and unorthodox way -- by a mix of actively and passively burning cigarettes in a continuous stream of air -- and caused blood COHb levels in the order of 28%. A month of daily exorbitant exposures resulted in some non-specific and mild pulmonary inflammation, but not in changes of pulmonary dynamics of pulmonary reactivity. The Proposed Rule failed to mention other studies in rats and beagles lasting as long as six months, which failed to

show any pulmonary function changes after exposure to main-stream smoke (Park et al., 1977; Coggins et al., 1980).

Thus, most experimental studies cited in the Proposed Rule are selective both in their choice and interpretation. From an objective point of view, the studies cited by the Proposed Rule -- as well as those not cited -- generate weak hypotheses impotent to sustain inferences of ETS risk for pulmonary function in humans. This conclusion is further confirmed by the epidemiologic, clinical, and experimental studies in humans mentioned above -- all pointing to active smoking threshold effects at doses much larger than possible ETS doses.

Cardiovascular. The Proposed Rule speculates about the "possible mechanistic effects" of nicotine and carbon monoxide (CO) on the cardiovascular system based on inferences from active smoking, while continuously ignoring dosimetry differentials. For instance, in regard to the possible aggravation of angina by CO, the Proposed Rule fails to mention that the National Academy report on ETS as well as EPA regulations consider that such effects may occur at COHb blood concentrations above 3% (NAS, 1986 p.261; USEPA, 1984). Because this is a risk management figure with an ample safety margin, the true threshold would obviously be much higher. In any event, a 3% COHb level is not reached even in extreme conditions of ETS exposure (NAS, 1986; Jarvis et al., 1983) and, while cumulative CO exposures in workplaces may exceed this level, adequate ventilation would obviously be the completely remedial solution.

It is not clear why the Proposed Rule mentions again the Olson study (1985) just reviewed under pulmonary effects above, other than to state that rats exposed to extraordinary smoke concentrations attain high COHb blood concentrations. This study is more remarkable for not having found pulmonary changes than otherwise. The much quoted study by Zhu et al.(1993) is equally remarkable for its lack of adverse findings. The rabbits in this study were exposed to extreme concentrations of what amounts to freshly diluted side-stream smoke, with particulate concentrations 100 times and 1000 times higher than for typical ETS at the low and high doses respectively, when considering that typical ETS particulate concentrations listed by the EPA are in the order of 30 $\mu\text{g}/\text{m}^3$ (USEPA 1992c). There was no effect on serum triglycerides, cholesterol, and high density lipoprotein cholesterol. Bleeding time *decreased* in the treated groups, as did platelet aggregation and platelet count in all groups, including controls. The "atheros-

clerotic" changes mentioned in the paper actually amounted to somewhat increased lipid deposits in the arterial walls, although the study does not provide the micrographs necessary for an independent evaluation. The pathognomic significance of such changes is unknown, given that they were similar in unexposed control animals and that no report is given of the likely effects of the stress induced by smoke exposure. Also, the results presented must be interpreted in the context of the natural predisposition of New Zealand rabbits to atherosclerosis, especially when fed a high cholesterol diet as in this study. Commendably, the Proposed Rule did not mention the Penn and Snyder study (1993), which produced even weaker and uninterpretable results in cockerels.

What the Proposed Rule could not quote are the results of a the largest, best planned and rigorously conducted inhalation study of cigarette smoke ever performed. This two year massive inhalation study was sponsored and directed by the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI), and initiated when the writer of the present comment was Director of the NCI-NHLBI Smoking and Health Program. It was performed between February 1978 and March 1980 on 220 purebred beagles fed a 5% cholesterol diet and exposed by tracheostomy to main-stream cigarette smoke variously spiked to provide excesses of nicotine or CO or of both (Hazleton, 1980). The study was designed and monitored by a group of top experts specifically assembled by NCI-NHLBI. After two years of exposure, the unexpected results gave unequivocal indication that increasing levels of cigarette smoke, CO and nicotine *reduced* the severity of atherosclerotic lesions. The final report concluded that "[t]hese results appear more indicative of a possible protective effect from cigarette smoking and/or CO inhalation than of an atherogenic effect". The study could not find incidental lesions of the respiratory system nor significant changes in blood lipids among the exposed groups.

Despite its impressive origins, impeccable technical conduct, and timely conclusion, the unexpected and anticlimactic results of the study likely advised against publication, which would have clashed with the then prevailing policies constraining both NCI and NHLBI. In any event, the study is presented here not as an apology for active smoking, but simply to illustrate the variability of animal experimental results, and their uncertain usefulness especially when human data about threshold effects are available and convincing in their own right.

Lung cancer. The just mentioned NCI-NHLBI inhalation study in beagles could not find preneoplastic or neoplastic lesions in the lungs or other tissues of the animals tested (Hazleton, 1980). The Proposed Rule mentions the Otto and Elmenhorst (1967) study, but fails to report that the differences observed after exposure to the gas phase of main-stream smoke were minor and not statistically significant, despite exposure at maximum tolerated doses. The mouse strains used have a history of high rates of spontaneous lung tumors, and despite this propensity the treated mice survived *longer* than the controls. Because of these and other inadequacies, this study provides no test of the possible carcinogenicity of the gas phase of main-stream smoke.

The Leuchtenberger and Leuchtenberger (1970) study is equally inadequate as a test of the main-stream smoke gas phase, because of the extremely elevated COHb levels attained and their effects on mortality; at 12 months, 92% of the controls survived, versus 60% for the main-stream exposed and 40% for the gas phase exposed mice. Such extreme conditions of unspecific toxicity could not be regarded as representative of even the highest active smoking regimens in humans. Similar caveats apply to the findings of Bernfeld et al.(1979), where the treated hamsters attained COHb blood levels on the order of 40%.

The Harris et al.(1974) study cited in the Proposed Rule does not sustain the suggestion of the carcinogenicity of the gas phase of main-stream smoke, while showing -- as other studies show -- that the smoke exposed animals survived as much as 14 weeks longer than controls. Davis et al. (1975) also failed to show main-stream gas phase carcinogenicity in Wistar rats. The extensive studies by Dontewill et al. (1973) failed to show any effects after massive exposure of Syrian hamsters to main-stream gas phase, and laryngeal leukoplakia alone -- but no tumors -- for exposure to main-stream smoke. A review by the International Agency for Research on Cancer concluded that "[e]xperiments on the carcinogenicity of the gas phase of cigarette smoke in hamsters and rats resulted in negative or inadequate findings..." (IARC, 1986, p.195).

Studies of direct lung implantation of smoke condensate pellets may have heuristic significance as research pieces, but little relevance to actual smoke exposure in humans (Stanton et al., 1972). Similar considerations are in order for the multitude of mouse skin painting experiments utilizing cigarette smoke condensates, which lack a rational basis for a qualitative and quantitative translation applicable to human conditions, whether by dosimetry, administration route, and clearance or metabolic dynamics.

The Proposed rule cites approvingly the detailed, extensive, and critical review by Mohr and Reznik (1978). This review, however, does not sustain the inferences of the Proposed Rule and actually concludes that "since experimental animals have notably failed to develop tumors under standard laboratory conditions, the possibility exists that the carcinogenic action of cigarette smoke as seen in humans could require the additional stimulus of other environmental factors. If this were to be the case, a high incidence of pulmonary tumors in experimental animals could never be expected." Experimental data offer no plausible argument to classify ETS as a human risk, and do not contradict the evidence of NOAELs for active smoking. The arbitrariness of *a priori* assumptions of ETS-related human risks is further underscored by equivocal and uninterpretable epidemiologic reports.

EPIDEMIOLOGIC STUDIES

Weak ETS exposures suggest that epidemiologic studies would at best produce weak risk associations. Recent reviews by the EPA and other ETS opponents have engaged in controversial meta-analysis exercises with combined estimates of apparent relative risk on the order of 1.15 - 1.30 for most of the associations investigated (USEPA, 1992c; Steenland, 1992). Because of the limited sensitivity of epidemiology, these levels are commonly recognized as extremely weak associations (Wynder, 1987; Rothman, 1982).

Besides, most of the reports are not statistically significant, several show no risk at all, and most are compatible with interpretations suggesting protective effects of ETS exposure. Straightforward logic considerations would accord much significance to studies reporting null or protective effects in the presence of ETS exposure -- at the very least they are strong evidence that factors other than ETS are likely to be operational in positive studies. The reasons for these contradictions become more apparent when considering that the diseases investigated -- lung cancer, cardiovascular, respiratory, and other diseases -- are multifactorial and depend on a complex web of risk factors that are probably peculiar to each individual. Other incurable problems stem from the inevitable uncertainties in determining exposures over lifetimes, and in the reporting biases of respondents and interviewers alike.

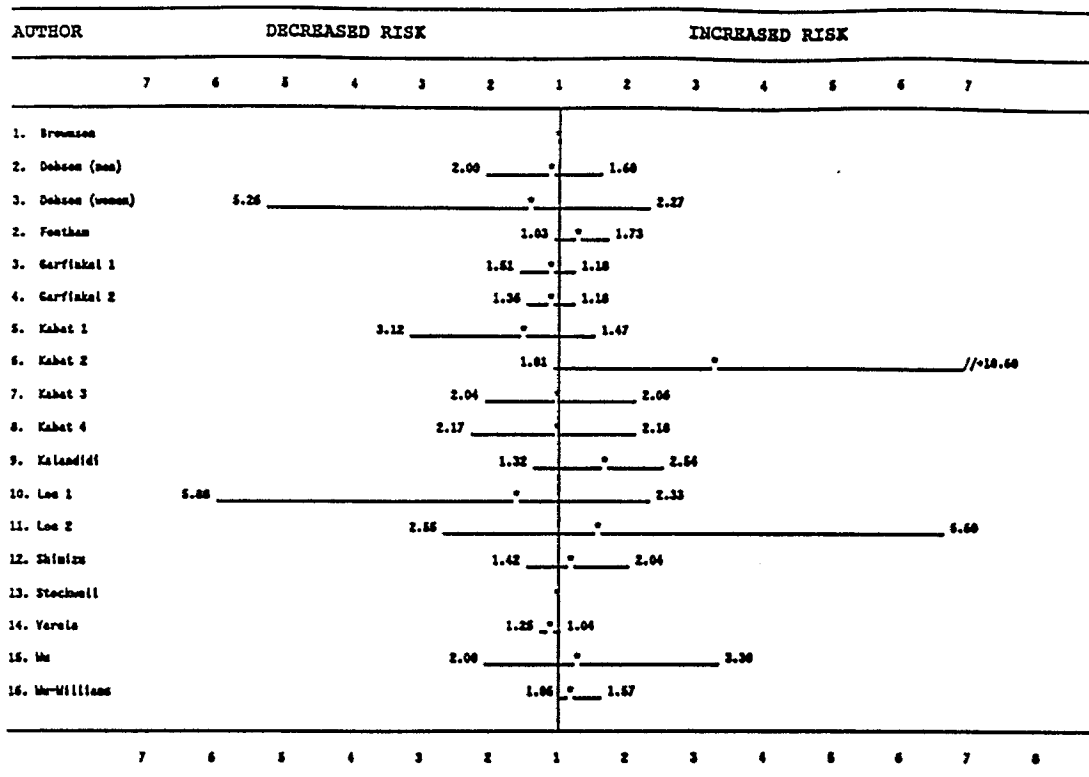
Lung Cancer. In 1986, the International Agency for Research on Cancer -- an arm of the World Health Organization -- was unable to validate a connection between ETS exposure and lung cancer, and stated that epidemiologic studies display "...substantial difficulties in [the] determination of passive exposure to tobacco smoke and to other possible risk factors.... The resulting errors could arguably have artificially depressed or raised estimated risks, and, as a consequence, each is compatible either with an increase or with an absence of risk." (IARC, 1986, p.308).

Today's data present the same weaknesses, as apparent from their listing in *Figures 1-4* (*). Of the studies available, one group considers people exposed to ETS at work, and shows no overall increase of lung cancer risk (*Figure 1*) (LeVois and Layard, 1994; Lee, 1992). A second group addresses people exposed to ETS at home since childhood, and the combined results also show no increase of lung cancer risk (*Figure 2*) (Lee, 1992). Giving no good reason, the EPA excluded these negative risk reports in its assessment (USEPA, 1992c).

A third group (*Figure 3*) involves over 30 international studies, addressing non-smoking wives exposed to the smoke of their husbands at home. Of these studies, less than half report a small risk elevation below statistical significance, some report no risk change, and about one third report a decrease of risk also below statistical significance (USEPA, 1992c; Lee, 1992). The EPA based its risk assessment on 11 US spousal exposure studies (*the first 11 in Figure 4*), none of which reports an overall statistically significant increase of risk at the 95% confidence level. Yet, the EPA states that its conclusions were "...based on the a priori hypothesis...that a positive association exists between exposure to ETS and lung cancer." (USEPA, 1992c, page 5-2). The Agency's prejudice materialized by adopting one-tailed statistics and reducing from $P=0.05$ to $P=0.10$ the meta-analysis significance of the combined studies.

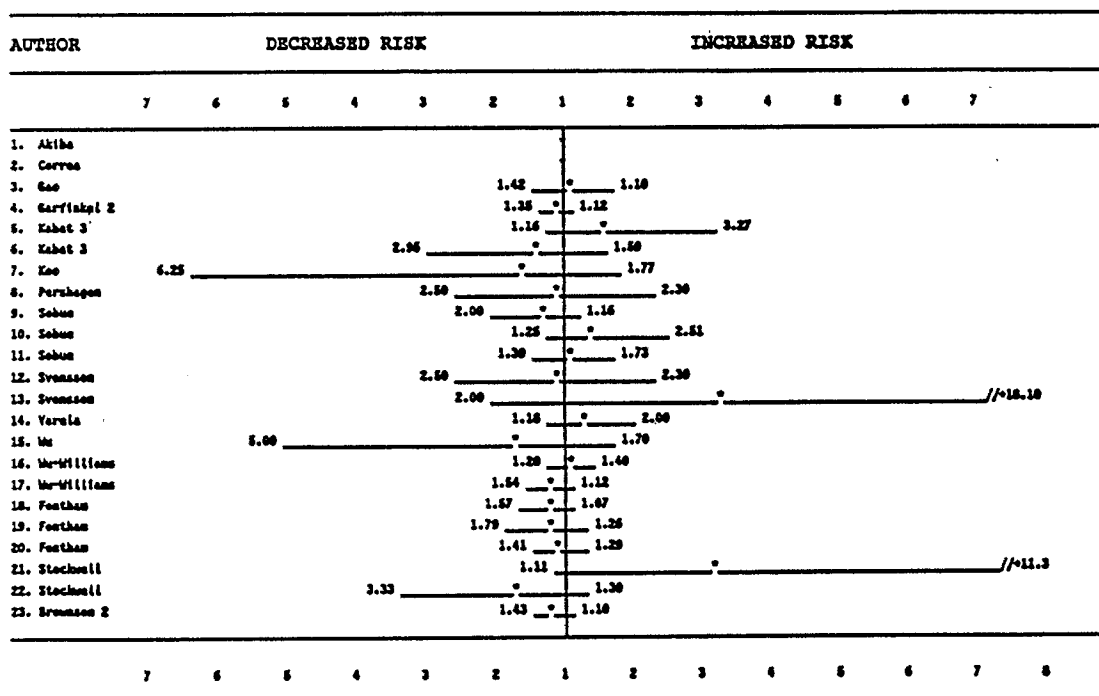
* NOTE ON FIGURES 1-4 and 6. The logarithmic analysis leading to relative risks (RR) or odd ratios (OR) confines reduced risk values to the interval from 0 to 1, while increased risk values span the interval from 1 to infinity. The correct visual representation requires that reduced and increased risk values be displayed on equivalent scales. The symmetry is achieved by giving reduced risk values as the reciprocals of the <1 values obtained logarithmically and as such reported in published studies. In Figures 1-6, the central vertical line represents the null risk value (value 1). Decreased risk values are to its left, increased risk values to its right. For each study cited, the star marks the midpoint estimate and the solid lines span the domain of the 95% confidence interval, if reported in the cited publications.

FIGURE 1. REPORTED INCREASED AND DECREASED LUNG CANCER RISK IN NEVER SMOKERS EXPOSED TO ENVIRONMENTAL TOBACCO SMOKE AT WORK



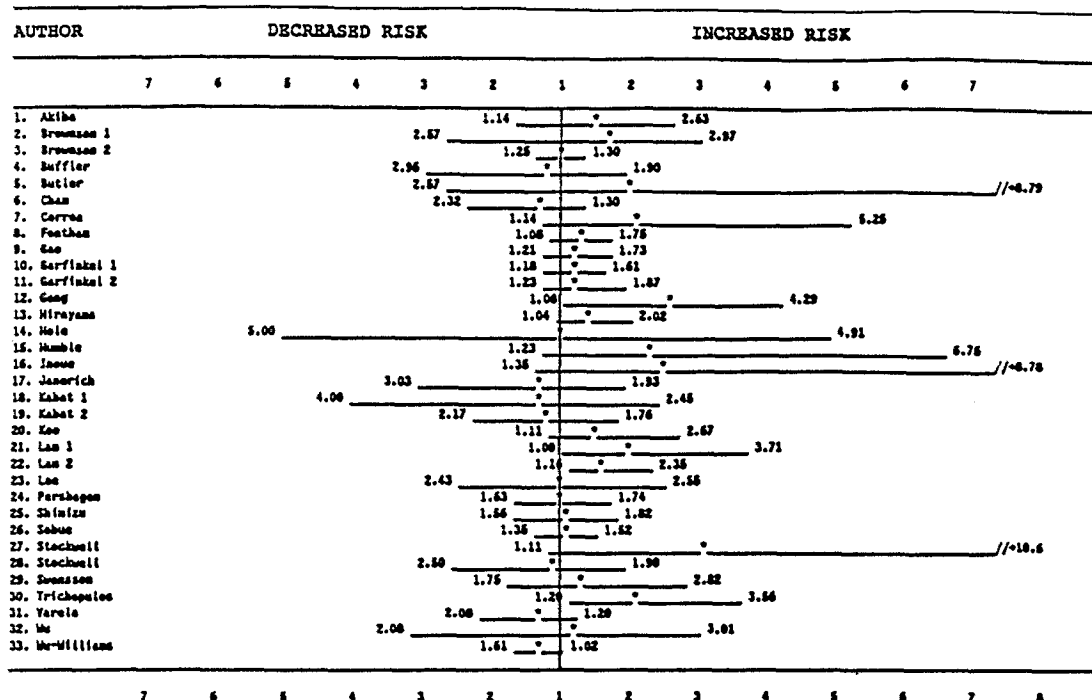
Data from : Lee, 1992; LeVeis and Lazard, 1994; Stockwell et al., 1992; Brownson et al., 1992; Dehnen et al., 1981.

FIGURE 2. REPORTED INCREASED AND DECREASED RISK OF LUNG CANCER IN NEVER SMOKERS EXPOSED TO ENVIRONMENTAL TOBACCO SMOKE DURING CHILDHOOD



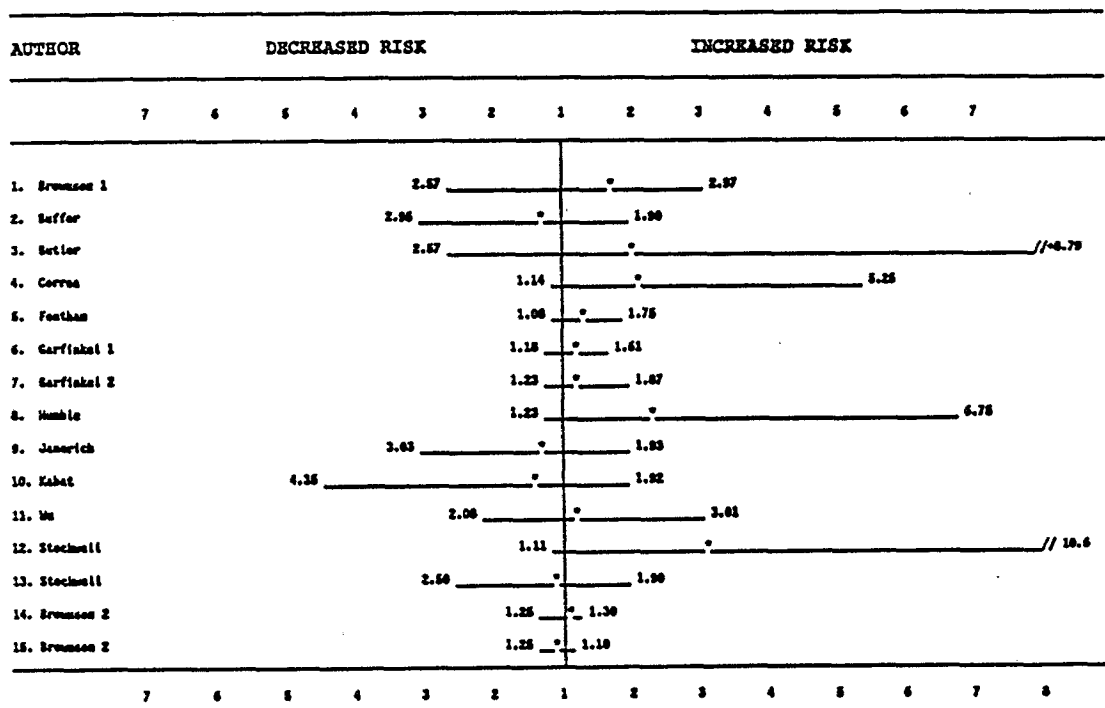
Data from : US EPA, 1992a; Lee, 1992; Stockwell et al., 1992; Brownson et al., 1992.

FIGURE 3. REPORTED LUNG CANCER RISK IN NEVER SMOKING FEMALES MARRIED TO SMOKERS



Data from : USEPA, 1992c; Lee, 1992; Stockwell et al., 1992; Brownson et al., 1992.

FIGURE 4. REPORTED INCREASED AND DECREASED RISK OF LUNG CANCER IN NEVER SMOKING US FEMALES MARRIED TO SMOKERS



Data from : USEPA, 1992c; Lee, 1992; Stockwell et al., 1992; Brownson et al., 1992.

The EPA also arbitrarily ignored the two latest studies, funded by the National Cancer Institute and reporting data that counter the Agency's conclusions when combined with the 11 studies considered (Stockwell et al., 1992; Brownson et al., 1992)).

Figure 5. Rank of reported lung cancer risks relative to the risk reported for ETS

| | |
|------------------------------|----|
| ETS | 1 |
| Hormone therapy | 7 |
| Motor exhaust | 8 |
| Phys. inactivity | 8 |
| Milk intake | 10 |
| Alcohol intake | 11 |
| β -carotene deficiency | 11 |
| Cholesterol | 11 |
| Cardiac anomalies | 12 |
| Low fruit | 12 |
| Pork meat intake | 12 |
| Occupation | 13 |
| Urban/rural | 14 |
| Psychosocial traits | 15 |
| Low vegetables | 16 |
| Beer drinking | 17 |
| Socioeconomic class | 19 |
| Ventilatory function | 20 |
| Radon | 21 |
| Family history | 26 |
| Cooking methods | 28 |
| Dietary fat | 30 |
| Tuberculosis | 50 |

Adapted from Gori and Mantel, 1991

The inconsistency of epidemiologic studies derives from the many problems they share. In the first place, it is difficult if not impossible to define retrospectively the lifetime exposure to ETS of any person, especially of deceased ones. Also, and despite much epidemiologic evidence to the contrary, EPA discounted other reported lung cancer risks -- differences in nutrition, disease experiences, physical activity, socioeconomic status, occupation, and others (*Figure 5*). These risks are much larger than the presumed ETS risk, appear to cluster preferentially in smoking households, and are more than capable of accounting for the small risk attributed to ETS (Gori and Mantel, 1991; Lee, 1992).

Several studies have shown that smokers in general display lifestyles that include peculiar risk factors other than smoking: for instance they may exercise less, consume more alcohol, have less healthy diets, and so on (Margetts and Jackson, 1993). Also, it is well documented that these less healthy habits and risks eventually extend to non-smoking members of a household (Gori and Mantel, 1991). With this in mind, it is no surprise that apparent risks for ETS exposure have been noted only in non-smoking wives of smokers. Other studies have consistently failed to report elevated risks in environments such as workplaces (Lee, 1992; Stockwell et al., 1992; Brownson et al., 1992; LeVois and Layard, 1994).

Studies of smoking and non-smoking households have shown that corrections for differences of beta carotene intake alone – a protective factor for lung cancer – can reduce to near statistical insignificance the risk attributed to ETS (Sidney et al., 1989; Le Marchand et al., 1989, 1991). Therefore, the slight apparent attributions of risk to ETS could easily disappear after cumulative correction for other risk factors known to cluster in smoking households.

Besides these confounding factors, important biases have been documented in ETS studies. Today, no one disputes that more "politically correct" studies are funded, and more reports hinting at increased risks are published than negative studies, thus giving disproportionate weight to increased risk reports. It is also documented that among the subjects of ETS epidemiologic studies 5-10% of those reporting as non-smokers are actually smokers. Correction for this bias alone virtually eliminates crude ETS-attributed risks (Lee, 1993). A further source of bias is the assumption about past common background exposures due to a presumably ubiquitous presence of ETS traces. This background assumption is not verifiable because the meaning of current data is uncertain, and information for the two or three decades preceding the epidemiologic surveys is unavailable. Arbitrary numerical values for this assumption have been nevertheless used for an upward adjustment of risk values (USEPA, 1992c).

Some glaring contradictions are emblematic. EPA justifies having disregarded workplace epidemiologic studies not because negative, but because EPA found them deficient in exposure determination -- unlike spousal data. Based on the same data, however, the Proposed Rule finds that ETS workplace exposures are equal to or greater than home spousal exposures. Supporters write approvingly of the Brownson, Stockwell, and Fontham studies, the latest large US studies (Stockwell et al, 1992; Brownson et al., 1992; Fontham et al., 1991). The Brownson abstract states that smoking restrictions in public and work places are well justified. Yet, the text reveals no overall risk, and explicitly speaks of no risk for workplace exposures, a finding shared with the Stockwell study but opposed by the Fontham study. All three studies agree that childhood exposures to ETS may *reduce* lung cancer risk, but the studies are discordant on histopathology results. The Stockwell study reports elevated risk for cases directly interviewed, but a *reduction* of risk if relatives were interviewed. Indeed, the list of contradictions extends to all available studies, as the IARC noted (IARC, 1986, p.308).

Thus, EPA's claim that ETS causes 3060 lung cancers a year is based on unwarranted assumptions, selective use of data, procedural manipulations, and the contrived illusion of mathematical precision (USEPA, 1992c)). Internal reviewers from the EPA Cincinnati laboratories were highly critical of the report (USEPA, 1992d). The Science Advisory Board itself advised the Agency against producing numerical estimates (Stolwijk, 1993), and Dr. Erich Bretthauer, then Associate Administrator for R&D at EPA, had to admit in official correspondence that the excess risk of lung cancer could be virtually zero (Bretthauer, 1992). A more recent assessment by the Congressional Research Service of the Library of Congress reached equally critical conclusions (Gravelle and Zimmermann, 1994).

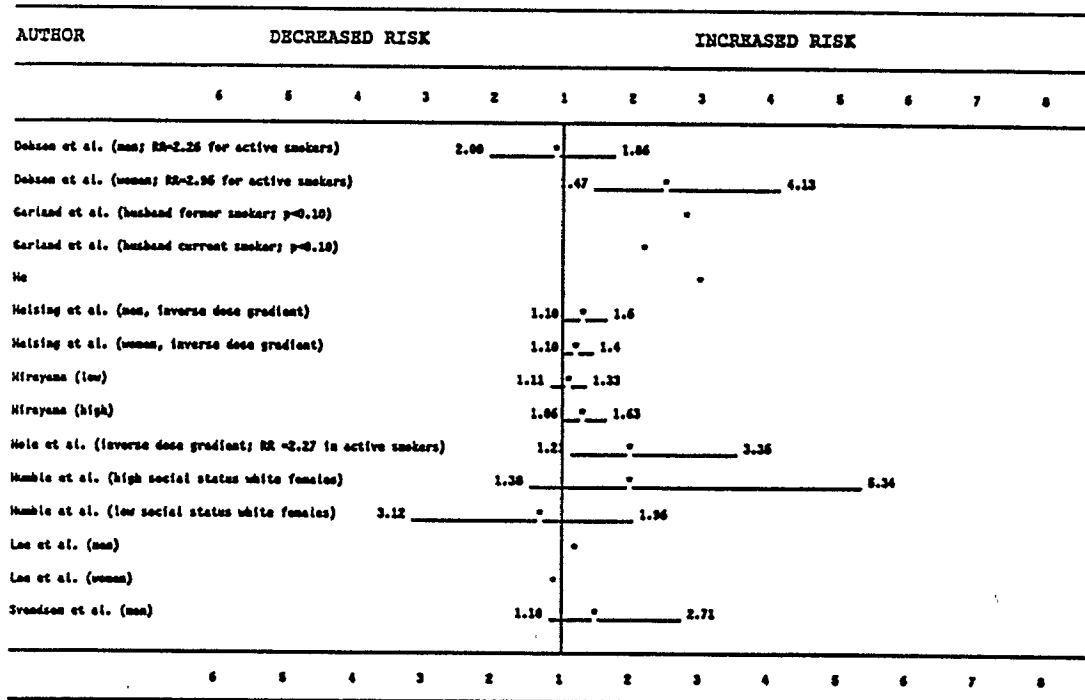
Accordingly, attributions of epidemiologic risk to ETS cannot be rationally sustained unless confounders and biases have been convincingly controlled, and adjustments have been objectively justified. Unfortunately, an accurate control of potential confounders and classification biases is probably beyond technical feasibility. ETS epidemiologic studies in general may not hold sufficient promise as profitable investments of scarce research funds. Simply stated, epidemiologic analysis may not be sensitive and specific enough to justify ETS investigations.

Cardiovascular Diseases. Earlier estimates, based on dosimetry differentials between active and passive smokers and related animal data, concluded that typical ETS exposures could not result in cardiovascular deficits (Schievelbein and Richter, 1984). Nevertheless, some 9 published reports have been used to suggest an association of ETS exposure and cardiovascular disease (*Figure 6*). Of these reports, four were analyzed and dismissed as uninterpretable by the National Academy review of ETS health effects (NAS, 1986, p.263-265). The Garland et al. report (1985) uses incorrect statistics and pools too small a sample of nonsmoking wives of smokers and former smokers. The Hirayama (1984) study did not adjust for misclassification bias and confounding risk factors. As the preceding Gillis et al. (1984) report, the Hole et al. study (1989) suffers from a small sample size and from lack of confounder control. The Swendsen et al. (1985) study also offers a small sample size and lacks statistical significance. Of the other studies, the Helsing et al. (1988) report suggests a small risk elevation, but the sample size is small and shows an inverse dose gradient. Lee et al. (1986) reported a reduced risk, while Humble et al. (1990) reported a risk that was increased or decreased depending on the socioeconomic status of the subjects. Dobson et al. (1991) reported

increased risk for women but decreased risk for men. All studies had small sample sizes, generally reported data that were not statistically significant, and mostly failed to control for misclassification biases and numerous confounding risk factors.

The combined excess risk from these nine cardiovascular studies has been estimates at 1.3 (Steenland, 1992). However, as seen above, several individual studies report no change in risk or reduced risk, some report inverse dose/response gradients, or relative risks for ETS exposures that are of the same magnitude as risks for active smoking (Figure 6).

FIGURE 6. REPORTED INCREASED AND DECREASED RISK OF CARDIOVASCULAR DISEASES IN NEVERSMOKERS EXPOSED TO ENVIRONMENTAL TOBACCO SMOKE



Data from: Dobson et al., 1991; Garland et al., 1986; He, 1988; Heising et al., 1988; Hirayama, 1984; Hole et al., 1988; Mumbe et al., 1988; Lee et al., 1986; Svendsen et al., 1987.

To further understand the meaning of these pooled values, it is important to recall that the apparent risk of cardiovascular diseases for active smokers is only 1.7 (Steenland, 1992). And even for active smokers there are solid reports of negative cardiovascular risks and threshold levels, as reviewed above.

Contradicting official EPA assertions, Steenland states that "arguments inferring ETS health effects based on known health effects of main-stream smoke...are not appropriate." Indeed, such inference would be disturbing because the apparent risk in active smokers is only slightly higher than the reported risk from ETS studies, despite vastly smaller ETS doses.

The closeness of the reported risk values indicates either the unlikely hypothesis of extreme differences in the specific biologic potencies of ETS and main-stream smoke, or the more plausible likelihood of interferences from confounding risk factors other than ETS. Steenland himself writes: "Due to the relatively slight increased risk of heart disease for passive smokers and the many factors known to affect heart disease, the possibility of uncontrolled confounding as a cause for the increased risk cannot be ruled out." (Steenland, 1992).

In fact, the role of confounders is certain, given that only a few of the nine studies of ETS and cardiovascular diseases have controlled for at most two or three of the over 250 risk factors reported in the literature (Hopkins and Williams, 1991). Nonetheless, setting aside all troubling considerations raised in his paper, Steenland attributes ischemic heart disease deaths to ETS with digital accuracy ranging from 74 to 18,390 units. Without explanation or supporting data, he assumes that the epidemiologic evidence is "reasonably accurate," that misclassifications and confounders are not "likely accounts for the observed risks," and that epidemiologic data are valid because "multiple studies are now consistent and reasonably well designed."

Objectively, these assumptions and conclusions are incompatible with the evidence. The consistency of some -- not all -- available studies can only be construed from a selective choice of reported data -- data that likely reflect consistent simplistic designs, consistent disregard of confounders, and consistent bias.

Respiratory Effects in adults. No link between ETS and respiratory diseases in adults has been established, despite many studies. The US Surgeon General Report on ETS (USSG, 1986) stated that "... a previously healthy individual would not develop chronic lung disease solely on the basis of [ETS exposure in adult life]". Regarding airflow obstruction, the same report noted "quite small" change in test subjects, and stated: "...it is unlikely that this change in airflow, per se, results in symptoms."